INVESTIGATION OF THE PRODUCTS OF THE REACTION OF EPICHLOROHYDRIN WITH AROMATIC AMINES

VI.* ACTION OF THIONYL CHLORIDE ON CHLORO AND CYANO DERIVATIVES OF 1,2,3,4-TETRAHYDRO-3-HYDROXYBENZO[f]QUINOLINE

S. I. Kutkevichus and R. I. Shablinskas

UDC 547.832+547.552:542.95

N-(γ-Chloro-β-hydroxy)propyl derivatives of 5-chloro-1-naphthylamine, 8-chloro-1-naphthylamine, and 5-cyano-1-naphthylamine were obtained. They were cyclized to 1,2,3,4-tetrahydro-3-hydroxy-7-chlorobenzo[f]quinoline (II), 1,2,3,4-tetrahydro-3-hydroxy-10-chlorobenzo-[f]quinoline (VII), and 1,2,3,4-tetrahydro-3-hydroxy-7-cyanobenzo[f]quinoline (X). Chlorination at the 6 position to form 1,2,3,4-tetrahydro-3-hydroxy-6,7-dichlorobenzo[f]quinoline occurs under the action of thionyl chloride on II at room temperature. The action of thionyl chloride on II, VII, and X at elevated temperatures leads not only to chlorination at the 6 position but also to aromatization of the tetrahydropyridine ring to form, respectively, 6,7-dichlorobenzo[f]quinoline (V), 6,10-dichlorobenzo[f]quinoline (VIII), and 6-chloro-7-cyanobenzo-[f]quinoline (XIII).

In developing previously published investigations [1-5] we have studied the action of thionyl chloride on 1,2,3,4-tetrahydro-3-hydroxy-7-chlorobenzo[f]quinoline (II), 1,2,3,4-tetrahydro-3-hydroxy-10-chlorobenzo[f]quinoline (VII), and 1,2,3,4-tetrahydro-3-hydroxy-7-cyanobenzo[f]quinoline (X).

The action of epichlorohydrin on 5-chloro-1-naphthylamine at 40-45°C gave N-(γ-chloro-β-hydroxypropyl)-5-chloro-1-naphthylamine (I), which was converted to 1,2,3,4-tetrahydro-3-hydroxy-7-chlorobenzo[f]quinoline hydrochloride by heating in chlorobenzene. The free base, 1,2,3,4-tetrahydro-3-hydroxy-7-chlorobenzo[f]quinoline (II), was obtained in 66% yield by treatment of an alcoholic solution of the hydrochloride with sodium hydroxide. This compound was also obtained by heating 5-chloro-1-naphthylamine with epichlorohydrin, as indicated in [6], but the yield in this process is somewhat lower (43%).

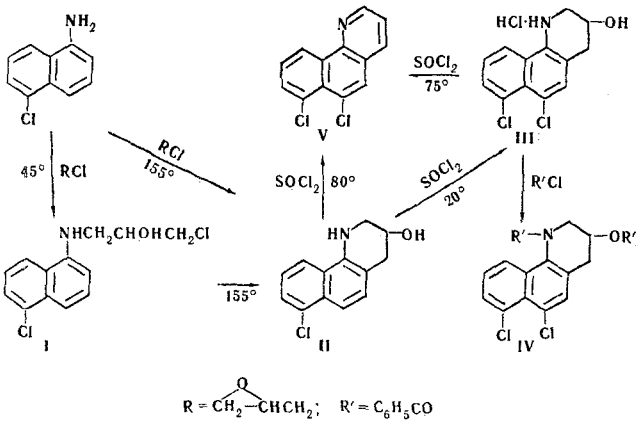
The action of thionyl chloride on II at room temperature gave 1,2,3,4-tetrahydro-3-hydroxy-6,7-dichlorobenzo[f]quinoline hydrochloride (III); the benzoate of 1,2,3,4-tetrahydro-N-benzoyl-3-hydroxy-6,7-dichlorobenzo [f]quinoline (IV) is obtained by benzoylation of it in pyridine with benzoyl chloride. At the same time, 6,7-dichlorobenzo[f]quinoline (V) is obtained by heating II or III with thionyl chloride. Consequently, II is chlorinated at the 6 position by the action of thionyl chloride on it at room temperature while, on heating, in addition to chlorination, the tetrahydropyridine ring is aromatized to give a dichloroderivative of benzo[f]quinoline.

1,2,3,4-Tetrahydro-3-hydroxy-10-chlorobenzo[f]quinoline (VII) was synthesized, like II, from N-(γ-chloro-β-hydroxypropyl)-8-chloro-1-napthylamine (VI) as well as from 8-chloro-1-napthylamine and epichlorohydrin [6]. 6,10-Dichlorobenzo[f]quinoline (VIII) was obtained by heating VII with thionyl chloride, i.e., chlorination occurred at the 6 position along with aromatization of the tetrahydropyridine ring. (See scheme on page 1421.)

Thus, the action of thionyl chloride on the monochloro derivatives of 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline gives dichlorobenzo[f]quinoline derivatives, and the second chlorine atom always enters

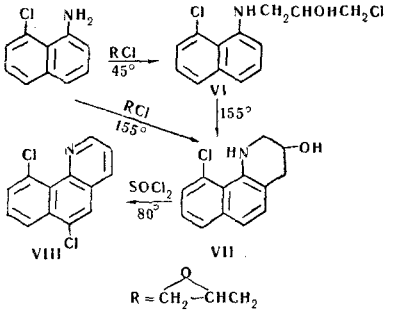
*See [5] for Communication V.

Kaunas Polytechnical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1522-1525, November, 1970. Original article submitted September 20, 1968.



the 6 position in the benzo[f]quinoline.

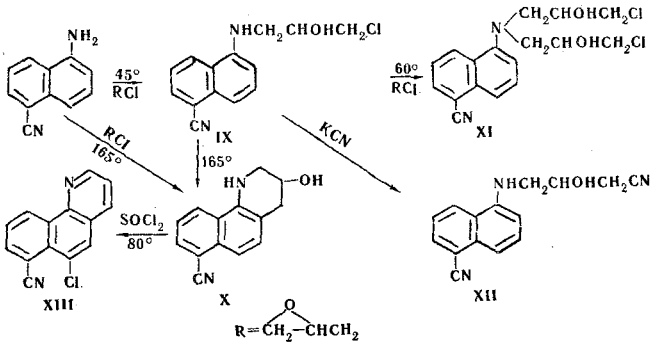
It was shown that N-(γ-chloro-β-hydroxypropyl)-5-cyano-1-naphthylamine (IX), which is identical to that obtained by heating 5-cyano-1-naphthylamine with epichlorohydrin in chlorobenzene, is formed in good yield by heating 5-cyano-1-naphthylamine with epichlorohydrin in glacial acetic acid at 45-50°, i.e., under the conditions for obtaining 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline and its derivatives.



1,2,3,4-Tetrahydro-3-hydroxy-7-cyanobenzo[f]quinoline (X) was obtained by heating 5-cyano-1-naphthylamine with epichlorohydrin to high temperatures in dichlorobenzene, by heating these starting compounds in a mixture of amyl alcohol and chlorobenzene in sealed ampules, as well as by heating IX in chlorobenzene, during which the cyclization of IX to X proceeds much more smoothly than the cyclization of the similar-in-structure I to II (the yield of II varies from 43 to 65.6%, while the yield of X ranges from 13 to 25%). Prolonged heating of IX with excess epichlorohydrin gives N,N-bis(γ-chloro-β-hydroxypropyl)-5-cyano-1-naphthylamine (XI), while heating of IX in methanol with potassium cyanide gives the nitrile of γ-(5-cyano-1-naphthylamino)-β-hydroxybutyronitrile (XII).

On the basis of the above it is apparent that introduction of a cyano group into the 5 position in 1-naphthylamine hinders not only replacement of the secondary hydrogen atom in the amino group by the γ-chloro-β-hydroxypropyl residue but also cyclization of IX to X.

6-Chloro-7-cyanobenzo[f]quinoline (XIII) is formed smoothly by heating X with thionyl chloride, i.e., introduction of a second-order substituent into the 7 position of 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline does not complicate the chlorination and aromatization with thionyl chloride.



EXPERIMENTAL

N-(γ-Chloro-β-hydroxypropyl)-5-chloro-1-napthylamine (I). A mixture of 17.8 g (0.1 mole) of 5-chloro-1-naphthylamine and 9.3 g (0.1 mole) of epichlorohydrin was heated for 3 days in a thermostat at 40-45°. The reaction mixture was then treated with 10 ml of methanol, and the resulting precipitate was filtered, washed with alchohol, and recrystallized from methanol to give 15.0 g (56%) of colorless needles of I with mp 79.5-80.0. Found %: Cl 26.2, 26.6. $C_{13}H_{13}Cl_2NO$. Calculated %: Cl 26.3.

1,2,3,4-Tetrahydro-3-hydroxy-7-chlorobenzo[f]quinoline (II). A mixture of 10.8 g (0.04 mole) of I and 10 ml of chlorobenzene was heated for 4 h at 150-155°. The resulting hydrochloride crystals were washed with chlorobenzene and dissolved in alcohol (50 ml). The solution was made alkaline with 25% aqueous sodium hydroxide and diluted with water (30 ml). Recrystallization from dilute alcohol gave 7.0 g (65.6%) of colorless crystals of II with mp 142.0-143.0.

II was also obtained by heating 5-chloro-1-naphthylamine with epichloro-hydrin in chlorobenzene [6]. The yield was 43%.

1,2,3,4-Tetrahydro-3-hydroxy-6,7-dichlorobenzo[f]quinoline Hydrochloride (III). A mixture of 4.6 g (0.02 mole) of II and 25 ml of thionyl chloride was held at room temperature for 1 h. The resulting precipitate was filtered, washed with ether, and recrystallized from methanol to give 5.0 g (93%) of crystals of III with mp 182° (decomp.). Found %: ionic chlorine 12.1. $C_{13}H_{11}Cl_2NO \cdot HCl$. Calculated %: ionic chlorine 11.6.

Benzoate of 1,2,3,4-Tetrahydro-N-benzoyl-3-hydroxy-6,7-dichlorobenzo[f]quinoline (IV). Compound III [1.1 g (0.004 mole)] was dissolved in 5 ml of pyridine, 3.8 g (0.03 mole) of benzoyl chloride was added, and the mixture was heated on a boiling water bath for 1 h. The reaction mixture was cooled, treated with 50 ml of 25% sulfuric acid, and diluted with water (40 ml). After decantation of the aqueous layer, the residual viscous oil was dissolved in ether and washed with sodium bicarbonate solution. After removal of the solvent, the residue was recrystallized from methanol to give 0.8 g (44%) of colorless needles of IV with mp 153.5-154.0°. Found %: Cl 14.3, 14.5. $C_{27}H_{19}Cl_2NO_3$. Calculated %: Cl 14.8.

6,7-Dichlorobenzo[f]quinoline (V). A. A mixture of 2.3 g (0.01 mole) of II and 10 ml of thionyl chloride was heated for 30 min at 75-80°. The reaction mixture was cooled, and the resulting precipitate was filtered and dissolved in methanol (150 ml). This solution was made alkaline with 25% aqueous sodium hydroxide and diluted with water (40 ml). The precipitate was filtered, washed with water, and recrystallized from alcohol to give 1.6 g (51%) of colorless needles of V with mp 142.0-143.0°. Found %: N 5.5, 5.4; Cl 28.2, 27.9. $C_{13}H_7Cl_2N$. Calculated %: N 5.6; Cl 28.5.

B. A mixture of 1.1 g (0.004 mole) of III and 6 ml of thionyl chloride was heated for 15 min at 75-80°. The precipitate was filtered and washed with thionyl chloride. Recrystallization from alcohol gave 0.6 g (60%) of colorless needles of V with mp 142.0-143.0. A mixed sample with crystals obtained in experiment A did not give a melting-point depression.

N-(γ-Chloro-β-hydroxypropyl)-8-chloro-1-naphthylamine (VI). This was obtained, like I, from 9.5 g (0.053 mole) of 8-chloro-1-naphthylamine and 5.5 g (0.06 mole) of epichlorohydrin. The product [7.0 g (48%)] was obtained in the form of white plates with mp 96.0-97.0°. Found %: Cl 26.1, 26.4. $C_{13}H_{13}Cl_3NO$. Calculated %: Cl 26.3.

1,2,3,4-Tetrahydro-3-hydroxy-10-chlorobenzo[f]quinoline (VII). This was synthesized, like II, from 6.8 g (0.025 mole) of VI in 6 ml of chlorobenzene. The product [3.5 g (50%)] was obtained in the form of colorless crystals with mp 115.0-116.0° (from methanol).

Compound VII was also obtained by heating 3.55 g (0.02 mole) of 8-chloro-1-naphthylamine with epichlorohydrin in chlorobenzene [6]. The yield was 1.5 g (32.6%).

6,10-Dichlorobenzo[f]quinoline (VIII). A mixture of 2.0 g (0.009 mole) of VI and 10 ml of thionyl chloride was heated for 1 h at 75-80°. After cooling, the precipitate was filtered, washed with methanol, and dissolved in alcohol. The solution was made alkaline with 25% sodium hydroxide, and the resulting precipitate of VIII was filtered, washed with water, and recrystallized from alcohol to give 0.9 g (43%) of a product with mp 153.0-154.0°. Found %: Cl 27.1, 27.5. $C_{13}H_7Cl_2N$. Calculated %: Cl 27.5.

N-(γ-Chloro-β-hydroxypropyl)-5-cyano-1-naphthylamine (IX). A mixture of 8.4 g (0.05 mole) of 5-cyano-1-naphthylamine [7], 4.6 g (0.05 mole) of epichlorohydrin, and 15 ml of glacial acetic acid was heated for 8 h at 45-50°. The resulting precipitate was filtered, washed with alcohol, and recrystallized from methanol to give 10 g (77%) of light-yellow crystals of IX with mp 127.0-127.5°. Found %: N 10.7, 10.9. $C_{14}H_{13}ClN_2O$. Calculated %: N 10.7.

1,2,3,4-Tetrahydro-3-hydroxy-5-cyanobenzo[f]quinoline (X). A. A mixture of 1.25 g (0.007 mole) of 5-cyano-1-naphthylamine, 2.5 ml of dichlorobenzene, and 0.68 g (0.007 mole) of epichlorohydrin was heated for 5 h at 165-170°. The resulting precipitate was filtered, washed with dichlorobenzene, and dried. It was then dissolved in alcohol (25 ml), and the solution was treated with 25% aqueous sodium hydroxide and diluted with water. Recrystallization of the precipitate from aqueous methanol gave 0.2 g (13%) of yellow plates of X with mp 173.0-173.5°. Found %: N 12.8, 12.7. $C_{14}H_{12}N_2O$. Calculated %: N 12.5.

B. A mixture of 5.0 g (0.03 mole) of 5-cyano-1-naphthylamine, 2.72 g (0.03 mole) of epichlorohydrin, and 10 ml of an amyl alcohol–chlorobenzene mixture (1 : 1) was heated for 7 h in sealed ampules at 170-175°. Compound X [1.2 g (25%)] was isolated as indicated in experiment A, and had mp 173.0-173.5°.

C. A mixture of 9.0 g (0.05 mole) of IX and 7 ml of dichlorobenzene was heated for 6 h at 165-170°. Compound X [1.5 g (13.7%)] was isolated as indicated in experiment A, and had mp 173.0-173.5°.

N,N-Bis(γ-chloro-β-hydroxypropyl)-5-cyano-1-naphthylamine Hydrochloride (XI). A mixture of 1.0 g (0.004 mole) of IX, 0.7 g (0.008 mole) of epichlorohydrin, and 15 ml of glacial acetic acid was held at 60-65° for 70 h in a thermostat (the end of the reaction was verified by chromatography). The reaction mixture was then treated with a sodium-acetate solution and extracted with chloroform. After removal of the solvent, the resulting oily substance was dissolved in ether, and the solution was saturated with hydrogen chloride. The resulting precipitate of XI was filtered, washed with ether, and recrystallized from alcohol to give 0.3 g (25%) of a product with mp 210° (decomp.). Found %: ionic chlorine 10.5. $C_{17}H_{18}Cl_2N_2O_2 \cdot HCl$. Calculated %: ionic chlorine 9.8.

γ-(5-Cyano-1-naphthylamino)-β-hydroxybutyronitrile (XII). A mixture of 5.2 g (0.02 mole) of IX, 10 ml of methanol, and 1.3 g (0.02 mole) of potassium cyanide was heated for 1 h at 70-75°. After removal of the solvent, the mass was treated with 70 ml of water and extracted with 100 ml of ether. After removal of the solvent, the residue was recrystallized from alcohol to give 4.0 g (80%) of light-yellow crystals of XII with mp 127.0-128.0°. Found %: N 16.2, 16.4. $C_{15}H_{13}N_3O$. Calculated %: N 16.7.

6-Chloro-7-cyanobenzo[f]quinoline (XIII). A mixture of 1.1 g (0.005 mole) of X and 5 ml of thionyl chloride was heated for 3 h at 80-85°. The resulting precipitate was filtered and dissolved in 35 ml of alcohol. This solution was made alkaline with 25% aqueous sodium hydroxide. The resulting precipitate was filtered and recrystallized from methanol to give 0.5 g (42%) of colorless needles with mp 236.5-237.5°. Found %: N 11.4, 11.5; Cl 14.6, 14.5. $C_{14}H_7ClN_2$. Calculated %: N 11.7; Cl 14.9.

LITERATURE CITED

1. N. N. Vorozhtsov, Jr., and S. I. Kutkevichus, Zh. Obshch. Khim., 28, 2682 (1958).
2. N. N. Vorozhtsov, Jr., and S. I. Kutkevichus, Materials of the Conference on Chemistry, Technology, and the Application of Pyridine and Quinoline Derivatives [in Russian], Riga (1957).
3. B. I. Milukas, S. I. Kutkevichus, and N. N. Vorozhtsov, Jr., Khim. Geterotsikl. Soedin., 554 (1965).
4. S. I. Kutkevichus, B. I. Milukas, and N. N. Vorozhtsov, Jr., Khim. Geterotsikl. Soedin., No. 1, 300 (1967).
5. S. I. Kutkevichus and R. I. Valite, Khim. Geterotsikl. Soedin., 969 (1970).
6. H. Lange and I. G. Farbenindustrie, Zetko Reports, FIAT, Microfilm C. 60, PBL 64079.
7. S. Gray and B. Jones, J. Chem. Soc., 680 (1954).